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Bristol’s Tyk2 ticks the boxes

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Bristol’s new oral psoriasis option looks much better than Otezla, but competing against injectables could be tricky.

Bristol Myers Squibb has long claimed that its oral Tyk2 inhibitor deucravacitinib has efficacy in line with biologics, but with improved convenience. Data released in psoriasis on Friday, however, suggest that the project has fallen short of these high expectations.

True, deucravacitinib comfortably outperformed its oral blockbuster counterpart Otezla in the Poetyk PSO-1 and 2 trials. And, perhaps more importantly, safety looked clean, a big consideration as Tyk2 is part of the Jak family. But the psoriasis arena is competitive and, on efficacy, deucravacitinib looks like a halfway house between Otezla and the forecast future market leaders, Abbvie’s Skyrizi and Novartis’s Cosentyx.

The sector looks set to get more competitive still: UCB’s bimekizumab is expected to be launched this year, and data reported in the *NEJM* on Friday suggest that it could become a fierce rival to deucravacitinib as well as to currently marketed psoriasis drugs.

Indeed, bimekizumab beat both Cosentyx and Abbvie’s autoimmune juggernaut Humira in the Be Radiant and Be Sure studies respectively. The findings from Be Radiant were particularly impressive: 62% of patients on bimekizumab achieved the primary endpoint of Pasi 100, or complete skin clearance, versus 49% of those on Cosentyx. The trade-off was an increase in oral candidiasis with bimekizumab.

Poetyk licence

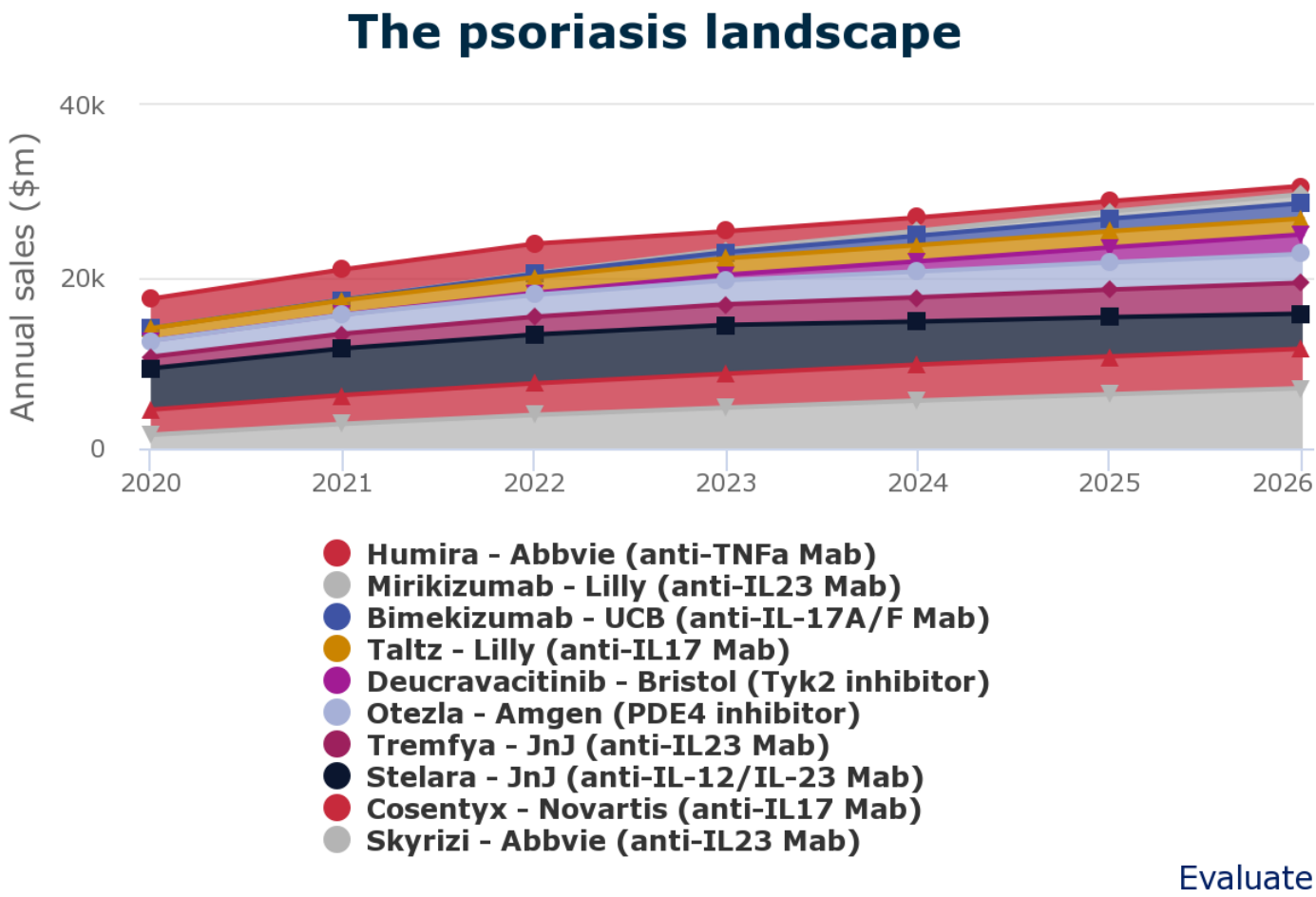
With the usual caveats about cross-trial comparisons, bimekizumab also looked better than deucravacitinib on Pasi 75, the primary endpoint of the phase 3 Poetyk PSO-1 and 2 studies of the Bristol agent. The Poetyk data were presented at the American Academy of Dermatology meeting on Friday.

On this measure, deucravacitinib also looks less effective than approved injectables like Skyrizi and Cosentyx.

Within and cross-trial comparison of selected psoriasis agents			
Product/project	**Company**	**Trial**	**Proportion of pts meeting Pasi 75**
Deucravacitinib	Bristol Myers Squibb	Poetyk PSO-1	59%^
		Poetyk PSO-2	54%^
Otezla	Amgen	Poetyk PSO-1	35%^
		Poetyk PSO-2	40%^
Bimekizumab	UCB	Be Radiant	71%*
		Be Sure	76%*
Skyrizi	Abbvie	Immhance	89%^
Cosentyx	Novartis	Erasure^^	82%**
		Fixture^^	76%**
*Note: Pasi 75 figures given at *4 weeks; **12 weeks; ^16 weeks; ^^scores given for 300mg dose only. Source: company releases, NEJM articles & product labels.*			

Perhaps this will not matter too much to Bristol. Should deucravacitinib be approved, its main rival will surely be Otezla.

And the Amgen drug – which Bristol offloaded when it bought Celgene – has carved out a sizeable niche despite unimpressive efficacy. Otezla sales are forecast to hit $3.4bn in 2026, according to *Evaluate Pharma*.



Deucravacitinib could soon be coming for a chunk of these. However, safety is still the big unknown for the Bristol project. One of Otezla's plus points is that it is seen as a safer alternative to injectables, as well as a more convenient one.

Meanwhile, the toxicity of Jak inhibitors is a major talking point, with the FDA recently postponing reviews of

Abbvie’s Rinvoq, Pfizer’s abrocitinib and Lilly and Incyte’s Olumiant in atopic dermatitis.Tyk2 is part of the Jak family, so there is a risk that deucravacitinib gets dragged into this debate.

On the basis of the project’s safety profile in Poetyk PSO-1 and 2 this seems unlikely. Rates of serious adverse events were similar between the deucravacitinib, Otezla and placebo arms, and there was no signal with deucravacitinib on malignancies, major adverse cardiovascular events, thromboses and infections, all of which have been seen with Jaks.

Tyks and Jaks

Stifel analysts believe that deucravacitinib could avoid the black box warning with which Jaks have been saddled.

However, this might not be the case for all the Tyk2s. Notably, deucravacitinib hits the regulatory or allosteric domain of Tyk2; as this domain differs across the Jak family, this approach is thought to be selective for Tyk2. Others taking a similar tack include Nimbus Therapeutics and Ventyx Biosciences, whose VTX-958 recently went into phase 1.

Meanwhile, Pfizer’s PF-06826647 hits the active or catalytic domain of Tky2. As this domain shares similarities across the Jak family, using it to target Tyk2 selectively has been tricky. Indeed, PF-06826647 is thought to have Jak2 activity. Pfizer has discontinued this project in ulcerative colitis, but development continues in psoriasis and hidradenitis suppurativa.

Galapagos also has a Tyk2 inhibitor, GLPG3667, in phase 1; according to Stifel, this also targets the active domain and could have Jak1 activity.

The risk/benefit profile of these agents might become clearer as data from more projects become available; Bristol itself has various trials of its Tyk2 ongoing in diseases including ulcerative colitis and Crohn's.

In psoriasis deucravacitinib's approval looks likely. The next job for Bristol is carving out a niche in a competitive sector.